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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,481	RABBANI ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009 and 22 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *251-287 and 625* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *251-287 and 625* is/are rejected.

7)☒ Claim(s) *251-254,276,277,282,287 and 625* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/17/09; 6/19/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response to the non-final rejection filed on June 22, 2009 and the response to the notice of non-compliant amendment filed on September 17, 2009 are acknowledged.

Claims 251-287 and 625 are currently pending.

The following include new grounds of rejection and also new grounds of objection. Any previously made rejections not reiterated below have been withdrawn. Applicant's arguments filed on June 19, 2009 with respect to the rejections made previously under 35 U.S.C. 103(a) have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section. Since the new grounds of rejection made in sections 6-11, 16, and 17 were not necessitated by Applicant's amendment, this Office Action is made **NON-FINAL**.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/896,897, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The earlier-filed '897 application does not provide adequate support for claims 251-287 and 625 of the instant application, because it does not teach primer extension using primers containing 3' terminal nucleotides that comprise nucleotide analogues with substitutions on the 2' position of the ribose ring. Accordingly, claims 251-287 and 625 have not been accorded benefit of the earlier-filed '897 application, and the instant application filing date (**October 24, 2003**) has been used for prior art purposes.

Information Disclosure Statement

3. Applicant's submission of an Information Disclosure Statement on June 19, 2009 is acknowledged. A signed copy is enclosed.

The information disclosure statement filed on September 17, 2009 fails to comply with 37 CFR 1.97(c), because it does not contain either a statement as specified in 37 CFR 1.97(e) or the fee set forth in 37 CFR 1.17(p). Accordingly, it has been placed in the application file, but the information referred to therein has not been considered.

Specification

4. The disclosure is objected to because of the following informalities: Figures 6 and 8-13 contain nucleic acid sequences that are greater than ten nucleotides in length, but have not been

identified by the appropriate sequence identifier either in the drawing figure or in the "Brief Description of the Drawings" section (see MPEP 2422.02). Also, pages 16, 17, 31-35, and 37-42 contain nucleic acid sequences that are greater than ten nucleotides in length, but have not been identified by the appropriate sequence identifier.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not appear to provide proper antecedent basis for the following elements of: **claim 261** (Sequenase, phi29 DNA polymerase, mutational variations of either Sequenase or phi29 DNA polymerase, and combinations comprising either of these enzymes), **claim 268** (arabinosides), **claims 278-280** (polymerase-mediated incorporation of nucleotides labeled with a phosphorescent compound, a chemiluminescent compound, a chelating compound, an electron dense compound, a magnetic compound, an intercalating compound, an energy transfer compound, an antibody, an antigen, a receptor, a hormone, an enzyme, and combinations comprising any of the aforementioned labels), and **claim 283** (glass slides or microtiter plates).

The use of the trademarks RNEASY, SUPERSCRIPT, and MINELUTE has been noted in this application (see at least page 31). These and any other trademarks in the specification should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Appropriate correction is required.

Claim Objections

5. Claim 251 is objected to because of the following informalities: This claim appears to contain a typographical error at the end of part (iv) where "and" is recited. It would appear that this word is unnecessary. Also, replacing the word "by" in line 1 of step (c) with "using" is suggested to improve the language of the claim.

Claim 252 is objected to because of the following informalities: This claim is grammatically incorrect. Replacing the word "are" in line with "is" and the word "are" in line 2 with "is" or "comprising" is suggested.

Claim 253 is objected to because of the following informalities: This claim contains typographical errors in line 2, where "copes" and "form" are recited. It would appear that "copies" and "from", respectively, were intended.

Claim 254 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 254 is drawn to the method of claim 252, wherein the homopolymeric sequences are present in the library of nucleic acid targets before or after isolation of the library from the biological source. Since the homopolymeric sequences must inherently be present in the library before or after the isolation step, claim 254 fails to further limit the method of claim 252.

Claim 276 is objected to because of the following informalities: This claim appears to be missing words, such as "the synthesis of", after the word "wherein" in line 1.

Claim 277 is objected to because of the following informalities: This claim contains a typographical error in line 2, where "nucleotides" is recited. It would appear that "nucleotide" was intended.

Claim 282 is objected to because of the following informalities: Replacing the words "primer or nucleic acid construct is" with "primers or nucleic acid constructs are" is suggested to maintain consistency with claim 251.

Claim 287 is objected to because of the following informalities: Replacing the word "segment" in line 3 with "sequence" is suggested to maintain consistency with claim 251.

Claim 287 is also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 287 is drawn to the method of claim 251, wherein at least one of the bases of the nucleotide analogues is different from the bases comprising the homopolymeric segment. Since the nucleotide analogues are part of primers that are complementary to the homopolymeric segment, the analogue bases would necessarily have to be different from the bases comprising the homopolymeric segment, as complementary base pairing would not occur otherwise. Accordingly, claim 287 does not appear to further limit the method of claim 251.

Claim 625 is objected to because of the following informalities: This claim contains minor typographical errors. The following changes are suggested: (a) replacing the words "comprise", "their", and "ends" in line 3 of step (ii) with "comprises", "the", and "end",

respectively, (b) inserting a hyphen between the words "template" and "dependent" in line 1 of step (iii), and (c) deleting the word "and" at the end of step (iii).

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 261, 277, 280, 283, 284, and 286 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 261 contains the trademark/trade names SEQUENASE, SENSISCRIPT, and OMNISCRIPT. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe particular polymerases and, accordingly, the identification/description is indefinite.

Claim 277 is vague and indefinite, because it is not clear from the claim language as to what nucleic acid must be copied in the presence of labeled nucleotides. Claim 277 is drawn to the method of claim 273, further comprising synthesizing a nucleic acid copy in the presence of at least one labeled nucleotide, thereby generating a labeled nucleic acid copy product. Claim

273 recites a step of conducting a transcription reaction, which generates a copy of a template nucleic acid. Claim 273 ultimately depends from claim 251, which also recites a nucleic acid copying step in step (c). As a result, the copying step recited in claim 277 could refer to the copying step in step (c) of claim 251, the transcription step of claim 273, or an additional copying step using the transcription product as a template. Since it is not clear from the claim language as to which of these nucleic acids must be copied, claim 277 is vague and indefinite.

Claim 280 is also indefinite, because it depends from claim 277.

Claim 283 is indefinite, because it depends from a canceled claim – clam 289. For examination purposes, claim 283 has been treated as depending from claim 282.

Claim 284 is indefinite, because it is unclear how a homopolymeric segment can be comprised of more than one type of nucleotide. Claim 284 is drawn to the method of claim 251, wherein the sequence of the homopolymeric segment is comprised of T, U, or any combination thereof. Since a homopolymeric sequence contains, by definition, only one type of nucleotide, it is unclear how a sequence comprised of T and U can be considered to constitute a homopolymeric sequence.

Claim 286 is vague and indefinite, because it is entirely unclear as to what the limitations recited therein are intended to encompass. Claim 286 is drawn to the method of claim 251, wherein at least one of the nucleotide analogues comprises a portion of the homopolymeric sequence. Since the primers that contain said nucleotide analogues are complementary to the homopolymeric sequence, it is unclear how a nucleotide analogue contained therein can "comprise a portion of the homopolymeric sequence" as required by claim 286.

Claim Rejections – 35 USC 112, 1st paragraph (Scope of Enablement)

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 278-280 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a polymerase to incorporate nucleotides having a fluorescent, phosphorescent, chemiluminescent, hapten, or intercalating label, does not reasonably provide enablement for using a polymerase to incorporate nucleotides having a label that is a chelating compound, an electron dense compound, a magnetic compound, an energy transfer compound other than fluorescent dyes, an antibody, an antigen, a receptor, a hormone, a ligand, an enzyme, or any combination thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 278-280 are drawn to the methods of claims 275-277, respectively, wherein the labeled nucleotides incorporated via polymerase activity are labeled with a fluorescent compound, a chemiluminescent compound, a phosphorescent compound, a chelating compound,

an electron dense compound, a magnetic compound, an intercalating compound, an energy transfer compound, an antibody, an antigen, a hapten, a receptor, a hormone, a ligand, an enayme, or any combination of the preceding. The claimed methods are classified in the unpredictable arts of chemistry and molecular biology and are associated with a high level of skill in the art.

The scope of claims 278-280 is very broad, because they encompass polymerase-mediated incorporation of a nucleotide conjugated to virtually any imaginable label. The labels encompassed by the claims have vastly different chemical structures and physical properties and would require the use of very different chemistries to be conjugated to nucleotides. The labels encompassed by the claims would also each present unique challenges with respect to polymerase-mediated incorporation.

As noted above in section 4, the specification only provides proper antecedent basis for polymerase-mediated incorporation of nucleotides attached to fluorescent labels or haptens, and accordingly, the disclosure of the instant application provides absolutely no guidance as to the methods for obtaining nucleotides conjugated to the above compounds or using them in a polymerase-mediated nucleic acid labeling reaction.

It was generally known in the art at the time of the invention that nucleotides conjugated to chemiuminescent compounds, fluorescent compounds, phosphorescent compounds, intercalating compounds, energy transfer compounds in the form of fluorescent dyes, and haptens could be used to label nucleic acids via polymerase-mediated nucleotide incorporation. (see, for example, paragraphs 45-51 of Lapidus et al. (US 2005/0100932 A1; newly cited)). The art also teaches that many polymerases are either unable to incorporate labeled nucleotides or are

only capable of low-efficiency incorporation, particularly when the label in question is large and "bulky" (see, for example, pages 2630 and 2634 of Giller et al. (Nucleic Acids Research (2003) 31(10): 2630-2635; newly cited)).

The quantity of experimentation necessary to practice the full scope of the claimed methods is very large. In order to practice the full scope of the claimed methods, the ordinary artisan would be required to undertake the following types of non-routine and unpredictable experimentation: (i) conjugating of nucleotides to each different type of label that was unconventional in the art, such as receptors and antibodies, which may include the development of novel methods of conjugation and (ii) demonstrating that polymerases are capable of incorporating each of the different resulting labeled nucleotides in a template-dependent process. Each different type of label encompassed by the claims presents different issues in terms of conjugation chemistry and likelihood of serving as a polymerase substrate. Given the lack of guidance in the art and the specification regarding the majority of the labels recited in the claims and the negative teachings in the art concerning polymerase-mediated incorporation of labeled nucleotides, this large amount of experimentation would necessarily be associated with a high degree of unpredictability. Accordingly, since a very large amount of highly unpredictable experimentation would be required in order to practice the full scope of the claimed methods, claims 278-280 fail to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph.

Claim Rejections – 35 USC 112, 1st paragraph (Written Description)

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 278-280 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The central inquiry when considering written description is whether an ordinary artisan would reasonably conclude that Applicant was in possession of the claimed invention at the time of filing (see MPEP 2163 and *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67, 43 USPQ2d 1398, 1404-05 (Fed. Cir. 1997); *Hyatt v. Boone*, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir. 1998)).

According to Revision 1 of the Written Description Training Materials (posted 4/11/08 at http://www.uspto.gov/web/menu/written/pdf), the following factors should be considered, when evaluating a claim for compliance with the written description requirement: (a) actual reduction to practice, (b) disclosure of drawings or structural chemical formulas (c) sufficient relevant identifying characteristics (d) method of making the claimed invention, (e) level of skill and knowledge in the art, and (f) predictability in the art (see page 1 of the Training Materials).

Claims 278-280 are drawn to the methods of claims 275-277, respectively, wherein the nucleotides incorporated via polymerase activity are labeled with a fluorescent compound, a

chemiluminescent compound, a phosphorescent compound, a chelating compound, an electron dense compound, a magnetic compound, an intercalating compound, an energy transfer compound, an antibody, an antigen, a hapten, a receptor, a hormone, a ligand, an enayme, or any combination of the preceding. The claimed methods are classified in the unpredictable arts of chemistry and molecular biology and are associated with a high level of skill in the art. As discussed above, the scope of claims 278-280 is very broad, because they encompass polymerase-mediated incorporation of a nucleotide conjugated to virtually any imaginable label. The labels encompassed by the claims have vastly different chemical structures and physical properties and would require the use of very different chemistries to be conjugated to nucleotides. The labels encompassed by the claims would also each present unique challenges with respect to polymerase-mediated incorporation.

As noted above in section 4, the specification only provides proper antecedent basis for polymerase-mediated incorporation of nucleotides attached to fluorescent labels or haptens, and accordingly, the disclosure of the instant application provides absolutely no guidance as to the methods for obtaining nucleotides conjugated to the above compounds or using them in a polymerase-mediated nucleic acid labeling reaction. As a result, the specification does not contain an actual reduction to practice of methods of using a polymerase to incorporate nucleotides labeled with a chelating compound, an electron dense compound, a magnetic compound, an energy transfer compound other than a fluorescent dye, an antibody, an antigen, a receptor, a hormone, a ligand, an enayme, or any combination of the preceding. The specification also fails to teach the relevant identifying characteristics required to satisfy the

written description requirement, since there is no discussion regarding methods for making or using such labeled nucleotides.

Since, as evidenced by the teachings of Giller (see above), many polymerases are either unable to incorporate labeled nucleotides or are only capable of low-efficiency incorporation, particularly when the label in question is large and "bulky", the polymerase-mediated incorporation of nucleotides labeled with the aforementioned labels is necessarily associated with a high degree of unpredictability and requires a high level of skill in the unpredictable arts of chemistry and molecular biology. Accordingly, it must be concluded that Applicant was not in possession of the full scope of the methods recited in claims 278-280 at the time of filing.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1 201 768 A2; cited previously).

These claims are drawn to method for copying a library of target nucleic acids using primers that are complementary to a homopolymeric sequence in the library of target nucleic acids and contain at least one nucleotide analogue at the 3'-terminus having a modification at the 2' position of the ribose ring.

Lin teaches methods for generating cDNA libraries from cells (see Figure 1 and column 2, line 42 – column 3, line 16).

Regarding claims 251, 264, and 281, Lin teaches a method for synthesizing one or more copies of a library of target nucleic acids comprising:

(a) providing:

(i) a library of target RNA molecules (see column 6, lines 10-17 and column 2, lines 45-51; see also Figure 1, step a),

(ii) primers comprising sequences complementary to homopolymeric sequences in the library of nucleic acid targets (see Figure 1, column 2, lines 52-56, column 6, lines 17-21 and lines 60-65),

(iii) synthesizing reagents for the synthesis of a nucleic acid copy (see column 2, lines 52-55 and column 6, lines 15-24), and

(iv) addition reagents for addition of a non-inherent universal detection target (UDT) comprising terminal deoxynuclsotidyl transferase (TdT) (column 2, lines 58-65 and column 6, lines 25-32),

(b) annealing the primers to the homopolymeric sequences in the library of target nucleic acids (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21)

(c) extending the annealed primers using the synthesizing reagents to generate at least one copy of the target nucleic acids (Figure 1, column 2, lines 52-56, and column 6, lines 17-21), and

(d) adding a non-inherent UDT to the extended primers (see Figure 1, column 2, lines 58-65, and column 6, lines 25-32, where the polyG tail is added to the extended primers).

Regarding claim 252, Lin teaches that the library of targets is isolated from a biological source (column 6, lines 15-17).

Regarding claims 254 and 256, Lin teaches that the homopolymeric sequences, which are poly A sequences, are present prior to the isolation of the library of targets from the biological source (see Figure 1, step a and column 6, lines 15-25).

Regarding claim 261, Lin teaches that the synthesizing reagents comprise Taq DNA polymerase (see column 7, line 5, for example).

Regarding claims 262 and 263, Lin teaches that the method of claim 251 further comprises:

(a) providing additional synthesizing reagents for synthesizing a complementary copy of the copy obtained in step (c) (see Figure 1, step c and column 6, lines 43-49)

(b) separating the nucleic acid target from the first nucleic acid copy (see Figure 1, step c and column 6, lines 43-49, where synthesis of the complementary copy by Pwo polymerase inherently results in separation of the target from the first copy)

(c) synthesizing the complementary copy using reverse primers complementary to sequences in the UDT (Figure 1, step c and column 6, lines 43-49, where the poly(dC) primer is taught).

Regarding claims 269-272, the forward and reverse primers taught by Lin comprise a production center, since they contain T7, T3, or SP6 promoter sequences which function to produce multiple copies of the target nucleic acid sequence (see Figure 1 and column 6, lines 15-65; see also column 3, lines 28-31).

Regarding claim 273, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55),

(b) providing dNTPs and NTPs (column 6, lines 35-55), and

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 275, Lin teaches condcucting the transcription reaction in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Regarding claim 285, Lin teaches that the homopolymeric segment is comprised of poly A (see Figure 1, column 3, lines 32-39, and column 6, lines 15-65).

Regarding claim 625, Lin teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(i) at least one nucleic acid target (see column 6, lines 10-17 and column 2, lines 45-51; see also Figure 1, step a),

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct comprises one or more terminal nucleotides at the 3' end (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21), and

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (column 2, lines 52-55 and column 6, lines 15-24),

(b) annealing the primer or nucleic acid construct to the target nucleic acid (see Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21), and

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21).

Lin does not teach that the primers contain 3' terminal nucleotides that are substituted with nucleotide analogues containing a modification at the 2' position of the ribose ring as required by claims 251, 259, 286, and 287. Lin also does not teach the use of chimeric primers as required by claim 260.

Laird teaches methods for conducting PCR amplification using modified primers (see abstract and paragraphs 12-18). Laird teaches that the disclosed modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (paragraph 37).

Regarding claims 251, 259, and 625, Laird teaches conducting PCR using primers in which 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-18).

Regarding claim 260, Laird teaches that the primers may contain additional nucleotide analogues (paragraph 20).

Regarding claim 286, the nucleotide analogues taught by Laird inherently comprise a portion (*e.g.* a sugar-phosphate backbone) of the homopolymeric sequence present in the library of nucleic acid targets.

Regarding claim 287, when incorporated into the oligo(dT) primers of Lin, the nucleotide analogues taught by Laird will necessarily have a base (thymine) that is different from the bases (adenine) comprising the homopolymeric sequence present in the library of nucleic acid targets.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Lin. An ordinary artisan would have been motivated to modify the primers taught by Lin to include the modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification stemming from primer-dimer formation or misextension of the primer (paragraph 37). Combining the teachings of Lin and Laird would result in placement of at least one of the nucleotide analogs in the homopolymeric sequence comprising the 3' oligo(dT) tail of the primer taught by Lin. An ordinary artisan would have had a reasonable expectation of success in applying the teachings of Laird to the method taught by Lin, since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the methods of claims 251, 252,

254, 256, 259-264, 269-273, 275, 281, 285-287, and 625 are *prima facie* obvious over Lin in view of Laird.

11. Claims 253, 255, 257, and 258 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Kustu et al. (US 6,242,189 B1; newly cited).

These claims are drawn to the method of claim 252, wherein the library comprises copies of nucleic acids isolated from a biological source and comprising a homopolymeric sequence enzymatically added after isolation of the library from the biological source.

The combined teachings of Lin and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625, as discussed above.

These combined teachings of Lin and Laird do not suggest that the library of nucleic acid targets is comprised of copies of nucleic acids isolated from a biological sample as required by claim 252. The combined teachings of Lin and Laird also do not suggest adding a homopolymeric sequence to the library of nucleic acid targets using an enzyme, such as TdT, after isolation of the nucleic acids from the biological sample as required by claims 254, 255, 257, and 258.

Kustu teaches methods for selectively isolating bacterial mRNA from biological samples (see abstract and column 1, lines 45-59). Kustu teaches that bacterial mRNAs do not usually contain a 3' polyA tail, and therefore, these mRNAs cannot be distinguished from rRNA or tRNA by a common structural feature (column 1, lines 9-27). The method of Kustu comprises isolating bacterial mRNA from a biological sample and adding a homopolymeric polyA tail to

the 3'-terminus of the isolated mRNA using TdT, a ligase, or polyA polymerase (column 1, lines 45-59 and column 2, line 10 – column 3, line 19). Kustu further teaches that the isolated mRNA can be amplified to permit for further analysis (columns 6-7).

It would have been *prima facie* obvious to apply the teachings of Kustu to the methods resulting from the combined teachings of Lin and Laird. Since Lin taught that the disclosed methods were suitable for use with any type of cell sample, an ordinary artisan would have been motivated to utilize any desired cell type when practicing the methods of Lin, such as the bacterial cells described in Kustu, with a reasonable expectation of success. When using mRNAs isolated from bacterial cells as the library of nucleic acid targets in the method of Lin, as suggested by the teachings of Kustu, an ordinary artisan would have been further motivated to conduct the polyA tailing reaction described by Kustu in order to prepare the bacterial mRNAs for the initial reverse transcription step in the methods of Lin. Thus, the methods of claims 253, 255, 257, and 258 are *prima facie* obvious in view of the combined teachings of the cited references.

12. Claims 265-268 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Willis et al. (US 6,858,412; cited previously) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052; cited previously).

These claims are drawn to the method of claim 264, further wherein a terminator nucleotide is provided in a mixture comprising terminator and non-terminator nucleotides during

the UDT addition step and the method further comprises synthesizing a copy of the nucleic acids obtained in the method of claim 251.

The combined teachings of Lin and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625, as discussed above.

Neither Lin nor Laird teaches including a terminator nucleotide in the TdT tailing reaction as required by claims 265-268.

Regarding claim 266, Lin teaches that the non-inherent UDT is added to a nucleic acid copy by providing TdT and non-terminator nucleotides (Figure 1, step c and column 6, lines 35-55).

Regarding claim 267, Lin teaches that the method of claim 266 further comprises:

(a) providing additional synthesizing reagents for the synthesis of a complementary copy of the nucleic acid copy (column 6, lines 35-55, where Pwo polymerase synthesizes a complementary copy of the UDT-containing copy)

(b) separating the target nucleic acid from the first nucleic acid copy (see Figure 1, step c and column 6, lines 35-55, where upon synthesis of the complementary copy, the target is inherently separated from the first copy)

(c) synthesizing the complementary copy (Figure 1, step c and column 6, lines 35-55).

Willis teaches amplification-based methods of nucleic acid analysis (see abstract and column 4, line 50 – column 5, line 15). Regarding claims 265, 266, and 268, Willis teaches the use of terminal transferase to add chain-terminating nucleotides, such as ddNTPs or acyclic nucleotides, to prevent extension or amplification (see column 26, lines 40-45).

Moran teaches that polymerase-mediated DNA and RNA synthesis reactions often produce molecules with non-homogenous or ragged 3' termini due to spurious template-independent addition of nucleotides by the polymerase (page 2044). Moran teaches that this "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." Regarding claims 265-267, Moran teaches that, "addition of a single non-coding nucleotide analogue to the 5' terminus of the template DNA strand can result in much more efficient and specific termination at the desired site (3'-end of the product). The use of such 'terminator' nucleotides results in the production of cleaner RNA and DNA oligonucleotide products, often in greater yields, and with more efficient use of nucleotides (page 2044, column 2 – page 2045, column 1)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Willis and Moran to the method resulting from the combined teachings of Lin and Laird. An ordinary artisan would have been motivated to include a terminator nucleotide, such as the dideoxy or acyclic nucleotides taught by Willis, in the terminal transferase tailing reaction taught by Lin, since Willis taught that these nucleotides prevented polymerase-mediated extension, and also since Moran taught that terminator nucleotides reduced template-independent addition of 3' terminal nucleotides by DNA and RNA polymerases (see column 46, lines 40-45 of Willis and pages 2044-2045 of Moran). An ordinary artisan would have been particularly motivated to minimize template-independent addition of nucleotides by the polymerase, since Moran taught that such addition "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." An ordinary artisan would have had a reasonable expectation of success in including

dideoxy or acyclic nucleotides in the terminal transferase reaction taught by Lin, since Willis taught that terminal transferase could incorporate these nucleotides into nucleic acids (column 26, lines 40-45). Thus, the methods of claims 265-268 are *prima facie* obvious in view of the combined teachings of Lin, Laird, Moran, and Willis.

13. Claims 274 and 276 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously).

These claims are drawn to the method of claim 271, wherein the RNA transcription step is conducted under conditions that result in a labeled DNA transcript or a labeled RNA/DNA chimeric transcript.

The combined teachings of Lin and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625, as discussed above.

Regarding claim 274, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55)

(b) providing dNTPs and NTPs (column 6, lines 35-55)

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 276, Lin teaches conducting the transcription reaction in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Lin does not teach the use of a mutated RNA polymerase for generation of a chimeric RNA/DNA transcript as required by claim 274.

Sousa teaches methods for synthesizing chimeric nucleic acid molecules using a mutant RNA polymerase (see abstract and column 4, line 53 – column 5, line 31).

Regarding claim 274, Sousa teaches providing reagents for RNA transcription comprising a mutated RNA polymerase, NTPs, & dNTPs and creating a chimeric DNA/RNA transcript (column 9, lines 41-46). Sousa further teaches that RNase A only cleaves RNA after a C or a U, and therefore, replacement of these rNMPs with dNMPs or other nucleotides resistant to nuclease cleavage would prevent this cleavage by RNase A (column 8, lines 55-67).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Sousa to the method resulting from the combined teachings of Lin and Laird. An ordinary artisan would have been motivated to utilize the mutant RNA polymerase taught by Sousa to generate chimeric DNA/RNA transcripts, since Sousa taught that such transcripts displayed improved resistance to ribonucleases (column 8, lines 55-67). An ordinary artisan would have recognized that RNase degradation of the transcription product produced in step (d) of the method outlined in Figure 1 of Lin would be detrimental, since the method of Lin required a post-transcription PCR amplification step, and therefore, would have been motivated to minimize the possibility of such degradation by generating a chimeric DNA/RNA transcript as suggested by Sousa. Thus, the methods of claims 274 and 276 are *prima facie* obvious in view of the combined teachings of Lin, Laird, and Sousa.

14. Claims 277, 278, and 280 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited

previously) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; cited previously).

Claim 277 is drawn to the method of claim 273 and has been interpreted as requiring the synthesis of a copy of the RNA transcript generated by the method of claim 273. Claims 278 and 280 are drawn to the methods of claims 275 and 277, respectively, and require the use of a labeled nucleotide selected from a Markush group.

The combined teachings of Lin and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625, as discussed above.

Regarding claim 277, although Lin teaches labeling nucleic acid amplification products at multiple stages of the method (transcription and TdT tailing – see column 5, lines 19-23), Lin does not teach including labeled nucleotides in the final RT-PCR amplification step used to generate a copy of the RNA transcription product as required by claim 277.

Regarding claims 278 and 280, Lin teaches labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Regarding claim 277, Steffens teaches including the labeled nucleotide in PCR reactions for incorporation into the resulting products (page 397, column 2). Regarding claims 278 and 280, Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin and Laird. An ordinary artisan would have been

motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin and Laird, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, the selection of a known material based on its suitability for the intended purpose is *prima facie* obvious in the absence of unexpected results. An ordinary artisan would also have been motivated to label nucleic acid products generated at any point in the method resulting from the combined teachings of Lin and Laird (*e.g.* the final RT-PCR step) in order to monitor the yield at each step of the process. An ordinary artisan would have been motivated to do so, since Lin taught labeling nucleic acid products produced at multiple steps of the method (see column 5, lines 19-23). As noted above, an ordinary artisan would have been motivated to utilize the fluorescently labeled nucleotide taught by Steffens to conduct this labeling step, since Steffens taught that the nucleotide permitted sensitive detection of labeled nucleic acids with minimal background. An ordinary artisan would have had a reasonable expectation of success in using the fluorescently labeled nucleotide taught by Steffens, since Steffens expressly taught its use in PCR amplification (page 397, column 2). Thus, the methods of claims 277, 278, and 280 are *prima facie* obvious in view of the combined teachings of Lin, Laird, and Steffens.

15. Claim 279 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; cited previously).

Claim 279 is drawn to the method of claim 276, respectively, and requires the use of a labeled nucleotide selected from a Markush group.

The combined teachings of Lin and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625, as discussed above.

Regarding claim 279, Lin teaches labeling transcription products using labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Steffens teaches including the labeled nucleotide in PCR and sequencing reactions for incorporation into the resulting products (pages 394-395). Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin, Laird, and Sousa. An ordinary artisan would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin, Laird, and Sousa, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, the selection of a known material based on its suitability for the intended purpose is *prima facie* obvious in the absence of unexpected results. In this case, an ordinary artisan would have had a reasonable expectation of success in using the fluorescently labeled nucleotide taught by Steffens in the labeling reaction of Lin, since Sousa taught that the disclosed mutant RNA polymerase

was capable of incorporating several different types of modified nucleotides (see column 9, lines 21-40). It is also noted that no evidence of unexpected results has been presented. Thus, the method of claim 279 is *prima facie* obvious in view of the combined teachings of Lin, Laird, Sousa and Steffens.

16. Claims 282 and 283 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Stinear et al. (Applied and Environmental Microbiology (1996) 62(9): 3385-3390; newly cited).

These claims are drawn to the method of claim 251, wherein the primers are immobilized on a solid matrix, such as a magnetic bead.

The combined teachings of Lin and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625, as discussed above.

The combined teachings of Lin and Laird do not suggest the use of bead-immobilized primers as required by claims 282 and 283.

Stinear teaches a method for isolating and amplifying mRNA from a biological sample (see abstract). The method of Stinear comprises capture of mRNA present in the sample using a magnetic bead-immobilized oligo(dT) primer followed by RT-PCR (see abstract and pages 3385-3387). Stinear teaches that capture of a target nucleic acid present in a sample using magnetic bead-immobilized oligonucleotides results in a greater reduction of amplification inhibitors than conventional purification methods (page 3385). Stinear also teaches that

"Magnetic beads are simple to use, do not require expensive equipment, and demonstrate a high level of recovery" (page 3388).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to practice the method resulting from the combined teachings of Lin and Laird using magnetic-bead immobilized oligo(dT) primers. An ordinary artisan would have been motivated to do so, since Stinear taught that magnetic bead-based capture and amplification was associated with reduced co-purification of amplification inhibitors and was a rapid, inexpensive, and simple method for capturing and amplifying a target nucleic acid of interest (see above). Since Stinear taught that the disclosed magnetic beads were commercially available (page 3386), an ordinary artisan would have had a reasonable expectation of success in conducting the methods resulting from the combined teachings of Lin and Laird using magnetic bead-immobilized primers as suggested by Stinear. Thus, the methods of claims 282 and 283 are *prima facie* obvious in view of the combined teachings of the cited references.

17. Claim 284 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Petrick et al. (Journal of Virological Methods (1997) 64: 147-159; newly cited).

Claim 284 is drawn to the method of claim 251, wherein the sequence of the homopolymeric segment is comprised of U, T, or a combination thereof.

The combined teachings of Lin and Laird render obvious the methods of claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625, as discussed above.

The combined teachings of Lin and Laird do not teach that the homopolymeric segment is comprised of U, T, or a combination thereof.

Petrick teaches a method for isolating and amplifying mRNA from HCV that comprises capture of the mRNA based on its unique polyU sequence followed by RT-PCR amplification (see abstract and pages 148-151). Petrick teaches that the 3'-terminal polyU region is unique to the HCV genome and permits HCV-specific mRNA capture (see abstract and page 148).

It would have been *prima facie* obvious to apply the teachings of Petrick to the methods resulting from the combined teachings of Lin and Laird. Since Lin taught that the disclosed methods were suitable for use with any type of RNA-containing sample, an ordinary artisan would have been motivated to utilize any desired sample type when practicing the methods of Lin, such as the HCV-containing samples described in Petrick, with a reasonable expectation of success. When using mRNAs isolated from HCV-containing samples as the library of nucleic acid targets in the method of Lin, as suggested by the teachings of Petrick, an ordinary artisan would have been further motivated to utilize the 3'-terminal polyU sequence, which is analogous to the 3'-terminal polyA sequence disclosed by Lin, as the homopolymeric region to which the primers are targeted, recognizing its suitability for the intended purpose. Accordingly, the method of claim 284 is *prima facie* obvious in view of the combined teachings of the cited references.

18. Claim 625 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borson et al. (PCR Methods and Applications (1992) 2: 144-148; cited previously) in view of Laird et al. (EP 1201788; cited previously).

Claim 625 is drawn to a method for synthesizing a copy of a target nucleic acid using primers that are complementary to a homopolymeric sequence in the library of target nucleic acids and contain at least one nucleotide analogue at the 3'-terminus having a modification at the 2' position of the ribose ring.

Borson teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(i) at least one nucleic acid target (p. 144, col. 3, "mRNA isolation" section)

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct comprises one or more terminal nucleotides at the 3' end (p. 144, col. 3, "Primer Design for cDNA synthesis" section, where the lock-docking primer contains a poly(T) region that is complementary to a poly A sequence in the target and two 3' terminal nucleotides)

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (p. 145, col. 1, "cDNA synthesis" section)

(b) annealing the primer or nucleic acid construct to the target nucleic acid (p. 145, col. 1, "cDNA synthesis" section)

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (p. 145, col. 1, "cDNA synthesis" section).

Borson does not teach that the 3' terminal nucleotide(s) of the primer contain 2' substitutions to the ribose ring.

Laird teaches PCR amplification using modified primers (see abstract and paragraphs 12-18). Regarding claim 625, Laird teaches conducting PCR using primers wherein 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-13). Laird teaches that the modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (see abstract and paragraph 37).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Borson. An ordinary artisan would have been motivated to modify the primer taught by Borson to include the modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification (paragraph 37). An ordinary artisan would have had a reasonable expectation of success applying the teachings of Laird to the method taught by Borson, since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the method of claim 625 is *prima facie* obvious in view of the combined teachings of Borson and Laird.

Response to Arguments

19. Applicant's arguments filed on June 22, 2009 have been fully considered, but they were not persuasive.

Regarding the rejection of claims 251-264, 269-273, 275, 281-286, and 625 under 35 U.S.C. 103(a) as being unpatentable over Lin in view of Laird, Applicant presents several arguments. These arguments have been fully considered, but they were not persuasive. This rejection currently applies to claims 251, 252, 254, 256, 259-264, 269-273, 275, 281, 285-287, and 625.

Applicant first states that the Laird reference is wholly concerned with eliminating non-specific primer extension resulting from the presence of non-target nucleic acids in the sample or primer-dimer formation by including modified nucleotides at the 3'-termini of the primers (pages 12-13). Accordingly, Applicant appears to argue at pages 12-13 that Laird is non-analogous art.

In response this argument that Laird is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the teachings of Laird, which pertain to methods for using nucleotide analogues to reduce non-specific amplification, are in the same field as Applicant's endeavor (nucleic acid amplification) and are also reasonably pertinent to the problem with which both the Applicant and Lin were concerned (*i.e.* amplification of a library of nucleic acid targets). Since Laird expressly defines non-specific amplification as any amplification other than that resulting from the hybridization of a primer to its complementary target sequence in a target nucleic acid (page 5, paragraph 28), and, since, as evidenced by Nam et al. at (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; newly cited - see Figure 1, for example), Jones et al. (Genome Research (2001) 11: 1346-1352;

cited previously – see page 1347), and Gregory et al. (Molecular and Biochemical Parasitology (1997) 87: 85-95; cited previously - see pages 90-91), poly(dT) containing primers, such as those used in the methods of Lin, were known to generate spurious reverse transcription products as a result of hybridization and extension from non-target internal polyA regions rather than the target 3'-terminal polyA region, the ordinary artisan would not have considered the teachings of Laird to be irrelevant to the methods disclosed by Lin. Accordingly, the Laird reference is not considered to constitute non-analogous art.

Applicant also argues that there is no motivation to apply the teachings of Laird to the methods disclosed by Lin, because the ordinary artisan would not have recognized any advantage from doing so (page 13). More specifically, Applicant argues that the methods of Lin comprise linear amplification and primers having a limited ability to hybridize to one another, and therefore, there is no need to eliminate primer-dimer formation (page 13). Applicant also argues that the Laird reference is directed to the amplification of specific target nucleic acids, whereas the Lin reference is directed to the amplification of a library of template nucleic acids, and therefore, there is no reason to apply the teachings of Laird to the global amplification method of Lin, since there are no "non-target" nucleic acids in the samples of Lin (pages 13-14). Applicant further notes that the only teachings in Laird relating to the general applicability of the method discuss application of the method to other types of amplification in which specific nucleic acids are to be amplified, and that no application to library amplification is discussed in Laird (page 14).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the

teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, as discussed above, an ordinary artisan would have been motivated to incorporate the 3'-terminal modifications taught by Laird into the poly(dT)-containing primers used to conduct the reverse transcription step in the method of Lin in order to reduce the possibility of nonspecific amplification during this step. Since Laird expressly defines non-specific amplification as any amplification other than that resulting from the hybridization of a primer to its complementary target sequence in a target nucleic acid (page 5, paragraph 28), and, since, as evidenced by Nam et al. at (Proceedings of the National Academy of Sciences, USA (2002) 99(9): 6152-6156; newly cited - see Figure 1, for example), Jones et al. (Genome Research (2001) 11: 1346-1352; cited previously – see page 1347), and Gregory et al. (Molecular and Biochemical Parasitology (1997) 87: 85-95; cited previously - see pages 90-91), poly(dT) containing primers, such as those used in the reverse transcription step of Lin, were known to generate spurious reverse transcription products as a result of hybridization and extension from non-target internal polyA regions rather than the target 3'-terminal polyA region, an ordinary artisan would have been motivated to incorporate the 3'-terminal modifications taught by Laird in order to reduce or eliminate this source of potential non-specific amplification in the method of Lin. Thus, although the samples amplified by the methods of Lin may not contain "non-target" nucleic acids in the sense argued by Applicant, they do possess non-target

regions in the form of internal polyA regions, and accordingly, nonspecific amplification is also a potential problem inherent in the methods of Lin.

Also, as discussed previously, Laird teaches that non-specific amplification can occur during the preparation of the amplification reaction mixture (paragraphs 4 and 28), and that use of primers having the disclosed 3'-terminal modifications can reduce this undesirable reaction (paragraphs 12-17, 28, and 47). Based on these teachings of Laird, an ordinary artisan also would have been motivated to incorporate the 3'-terminal modifications taught by Laird in the reverse transcription primers of Lin in order to minimize the possibility of non-specific amplification occurring during the setup of the reverse transcription reactions.

Accordingly, the ordinary artisan would have recognized a clear advantage in modifying the primers of Lin to contain one of the 3'-terminal modifications disclosed by Laird, specifically reducing the possibility of non-specific amplification stemming from misextension of the poly(dT)-containing primer or occurring during the reaction setup, and therefore, would have been motivated to incorporate the 3'-terminal modifications disclosed by Laird into the primers of Lin to obtain this advantage.

Finally, it is noted that the prior art is relevant for all that it contains or would have suggested to the ordinary artisan (MPEP 2123). In this case, as discussed above, Laird does not limit the use of the modified primers to any particular type of amplification method, stating, "However, the invention is not restricted to any particular amplification system. The use of the modified primers in other primer-based amplification methods in which primer-dimer or non-specific amplification product can be formed is expected to be useful (page 7, paragraph 47)." Laird also defined non-specific amplification as any amplification other than that resulting from

the hybridization of a primer to its complementary target sequence in a target nucleic acid (page 5, paragraph 28). Based on these teachings of Laird, an ordinary artisan would have been motivated to use primers containing the 3'-terminal modifications disclosed by Laird in any nucleic acid amplification reaction in which non-specific amplification was known to occur, such as the reverse transcription step conducted in the method of Lin, with a reasonable expectation of success.

Applicant further argues that the ordinary artisan would not have had a reasonable expectation of success in combining the teachings of Lin and Laird, since the criteria for "success" defined in the rejection are irrelevant to the methods disclosed by Lin (page 14).

This argument was not persuasive, because as discussed above, non-specific amplification was known to be a problem in reverse transcription reactions, such as those conducted by Lin. Accordingly, an ordinary artisan would have been motivated to apply the teachings of Laird pertaining to methods of reducing non-specific amplification to the methods of Lin in order to obtain a more specific reverse transcription step.

Finally, Applicant argues that claimed methods are associated with unexpected results, specifically the fact that incorporation of terminally modified nucleotides into primers designed to amplify a library of target nucleic acids can prevent the undesired extension by terminal transferase of extended primers remaining after first-strand cDNA synthesis and also increased amplification reaction product yields (page 14). This argument was not persuasive, because these benefits do not appear to be unexpected based on the teachings of Laird. It is also noted that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the

differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Since Applicant's arguments were not persuasive, the rejection has been maintained.

Applicant's arguments regarding the rejections of claims 265-268, 274, 276-280, and 287 made under 35 U.S.C. 103(a) citing Lin and Laird as the primary combination of references have been fully considered, but they were not persuasive. In the new grounds of rejection above, claims 253, 255, 257, 258, 265-268, 274, 276-280, and 282-284 have been rejected under 35 U.S.C. 103(a) citing Lin and Laird as the primary combination of references.

Applicant argues that the primary combination of references (Lin & Laird) does not render the method of independent claim 251 obvious, and that the additional secondary references cited in the rejections do not address this deficiency in the primary combination of references (see pages 14-17). This argument was not persuasive, because as discussed above, the combined teachings of Lin and Laird render obvious the method of independent claim 251. Since Applicant's arguments were not persuasive, the rejections have been maintained with modifications.

Applicant's arguments regarding the rejection of claim 625 under 35 U.S.C. 103(a) as being unpatentable over Borson in view of Laird have been fully considered, but they were not persuasive. Applicant argues that the rejection is improper because of the deficiencies in the Laird reference that have been described on pages 12-14 of the response (see page 17). Applicant's arguments regarding the teachings of Laird were not persuasive for the reasons set forth above. It is further noted that the method of claim 625 is not limited to library amplification, and therefore, not all of Applicant's arguments presented with regard to the Lin

and Laird reference are relevant to the rejection of claim 625. Since Applicant's arguments were not persuasive, the rejection of claim 625 under 35 U.S.C. 103(a) as being unpatentable over Borson in view of Laird has been maintained.

Conclusion

20. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Angela M Bertagna/
Examiner, Art Unit 1637